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A Nomogram for Predicting the Likelihood of Additional Nodal Metastases in Breast Cancer Patients With a Positive Sentinel Node Biopsy

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Background: The standard of care for breast cancer patients with sentinel lymph node (SLN) metastases includes complete axillary lymph node dissection (ALND). However, many question the need for complete ALND in every patient with detectable SLN metastases, particularly those perceived to have a low risk of non-SLN metastases. Accurate estimates of the likelihood of additional disease in the axilla could assist greatly in decision-making regarding further treatment.

Methods: Pathological features of the primary tumor and SLN metastases of 702 patients who underwent complete ALND were assessed with multivariable logistic regression to predict the presence of additional disease in the non-SLNs of these patients. A nomogram was created using pathological size, tumor type and nuclear grade, lymphovascular invasion, multifocality, and estrogen-receptor status of the primary tumor; method of detection of SLN metastases; number of positive SLNs; and number of negative SLNs. The model was subsequently applied prospectively to 373 patients.

Results: The nomogram for the retrospective population was accurate and discriminating, with an area under the receiver operating characteristic (ROC) curve of 0.76. When applied to the prospective group, the model accurately predicted likelihood of non-SLN disease (ROC, 0.77).

Conclusions: We have developed a user-friendly nomogram that uses information commonly available to the surgeon to easily and accurately calculate the likelihood of having additional, non-SLN metastases for an individual patient.

Key Words: Axillary metastases—Breast cancer—Nomogram—Prediction—Sentinel node.

The sentinel lymph node (SLN) biopsy procedure has been validated by numerous studies[1–6] and found to be accurate for assessing regional lymph node involvement. For those whose SLN biopsy specimen is histopathologically negative, the risk of "missed" axillary disease is extremely low.[7,8] Therefore, SLN biopsy alone, without complete axillary lymph node dissection (ALND), has been adopted at many institutions as an accurate method of staging the axilla while avoiding much of the morbidity associated with a complete ALND. Although the standard of care for breast cancer patients with SLN metastases remains performance of complete ALND, many question the need for complete ALND in every patient with detectable SLN metastases, particularly those in whom the perceived risk of additional disease is low.[9,10]

Proponents of performance of completion ALND after a positive SLN biopsy argue that further axillary clearance is critical to management. The total number of

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involved nodes is important prognostic information, as an increasing number of positive nodes portends worse survival.[11–13] This is reflected in the new American Joint Committee on Cancer (AJCC) sixth edition staging system, wherein the number of positive nodes defines N1, N2, and N3 disease and ultimately the stage to which the patient is assigned.[14] In addition, proponents of the performance of complete ALND after positive SLN biopsy argue that the additional information can benefit patients by guiding decisions about adjuvant chemotherapy. For the approximately one-half of patients in whom there is residual nodal disease, it is also argued that complete ALND can influence survival via local-regional control of the axilla,[15–17] thereby eliminating a potential site of recurrent disease and, ultimately, a source for distant disease. A meta-analysis of randomized trials revealed a 5.4% survival benefit associated with ALND for clinically node-negative patients.[18]

Opponents of complete ALND performed after positive SLN biopsy argue that the therapeutic benefit of complete ALND is minimal.[19] Furthermore, approximately 50% of patients with positive SLNs are found to have no other nodal metastases.[1–6,20–24] Therefore, many patients are undergoing unnecessary ALND, with no additional therapeutic benefit or further staging information provided. It is also argued that because patients with SLN metastases will generally receive systemic therapy, regardless of the presence of any additional nodal metastases, any residual disease does not influence choice of therapy and may itself be eradicated by the systemic therapy. In addition, radiation therapy after breast-conserving surgery may contribute to control of any additional nodal disease. It is this debate that physicians and their patients are faced with in the office setting when a positive SLN is discovered on final pathology.

Several groups have identified histopathological variables of the primary tumor and its metastasis that can influence risk of additional disease in the non-SLNs[9,10,21–29] (Table 1). Size of the primary tumor and size of the SLN metastasis are the two variables most commonly analyzed. Previous investigation at our institution found that size of the primary tumor and of the SLN metastasis are significantly predictive of likelihood of additional, non-SLN metastases.[26] Most other studies that examined at least one of these two variables showed a statistically significant correlation with risk of additional, non-SLN disease,[9,10,21–25,27–29] yet most have not been able to identify a subset that has no risk of additional disease in the non-SLNs.[10,22–24,27,28,30] Those studies that have identified favorable subsets with an apparently negligible risk of additional nodal disease have all involved very small subsets (i.e., 5–24 patients).[9,21,26,30–32]

Furthermore, it is difficult to estimate the risk of additional, non-SLN metastases for an individual patient by using the literature. First, the estimates of risk for any given characteristic vary considerably among studies. Tables 2 through 5 show reported incidences by primary tumor size, presence of lymphovascular invasion (LVI) in the primary tumor size of SLN metastasis, and presence of immunohistochemically (IHC-) detected SLN metastases. This variation in reported incidences may be attributable to relatively small sample sizes or the result of differences among the study populations in terms of other variables influencing risk. Second, it is difficult to apply risk estimates to several patient characteristics

TABLE 1. *Studies reporting predictors of non-SLN metastases in patients with a positive SLN biopsy; values listed are P values reported in study*

Study			Primary tumor characteristics					SLN charactertistics		
Author	Year	n	Size (cm)	Nuclear grade	Lymphovascular invasion	Multifocality	Estrogen receptor status	Method of detection	Size of SLN met	No. of positive SLN	No. of negative SLN examined
[a]Chu[9]	1999	157	.014	NS	NS	—	NS	NS	<.0001	NS	—
[a]Reynolds[21]	1999	60	.0004	NS	NS	—	.03	—	.002	—	—
Teng[22]	2000	26	.001	—	—	—	—	.02	—	—	—
[a]Turner[25]	2000	194	.03	NS	.03	—	NS	—	.01	NS	—
Abdessalam[23]	2001	100	NS	NS	.004	—	NS	—	.01	NS	—
Kamath[10]	2001	101	.005	—	—	—	—	—	.001	—	—
Rahusen[24]	2001	93	NS	NS	NS	—	NS	—	.05	.002	—
[a]Viale[28]	2001	109	NS	NS	NS	—	NS	—	.02	—	—
[a]Weiser[26]	2001	206	.007	NS	NS	—	—	—	.0002	—	—
[a]Wong[27]	2001	389	<.001	—	—	—	—	—	—	<.001	—
[a]Sachdev[29]	2002	55	.0001	—	.001	—	—	—	.02	—	—

NS, not statistically significant; —, not included in analysis. n, number of patients with positive SLN biopsy and complete axillary dissection; SLN, sentinel lymph node.

[a] Denotes studies reporting *P* values for multivariate analysis.

TABLE 2. *Studies reporting incidence of non-SLN metastases in axillae with positive SLN(s), by primary tumor size*

Author	T1a (≤.5 cm)	T1b (.6–1.0 cm)	T1c (1.1–2.0 cm)	T2 (2.1–5.0 cm)	T3 (>5.0 cm)
Chu[9]	0%	13%	29%	38%	71%
Reynolds[21]	[———	25% for T1	———]	[——— 79% for T2/3 ———	]
Turner[25]	17%	20%	46%	48%	73%
Kamath[10]	25%	30%	40%	46%	80%
Rahusen[24]	50%	50%	49%	50%	—
Weiser[26]	8%	21%	37%	48%	—
Wong[27]	14%	22%	30%	45%	57%
Viale[28]	100%	14%	25%	24%	—
Sachdev[29]	[———	13% for T1	———]	[——— 33% for ≥T2 ———	]
Mignotte[30]	[——— 14% ———	]	54%	52%	—

SLN, sentinel lymph node.

simultaneously because of the generally univariate method of reporting in the literature.

In an attempt to achieve a more precise prediction for the individual patient than is readily available by using these published estimates of risk, we used a multivariable logistic-regression analysis of a large data set to model the association between selected variables and the likelihood of metastases in non-SLNs in patients with a positive SLN biopsy. We examined pathological size of the primary tumor, the method of detection of the SLN metastasis, and several other variables that are readily available and theoretically related to risk of additional nodal disease. We used 702 cases from our large prospective sentinel lymph node database to develop the model, and we developed a user-friendly nomogram to predict the likelihood of finding additional positive nodes at completion ALND. We then tested our model by prospectively applying it in an additional study group comprising 373 patients.

The goal of our study was to develop a tool that would allow greater individualization of a patient's risk estimate by simultaneously taking into account several pertinent characteristics specific to the patient. With a more precise and individualized estimate, both physician and patient would be better able to weigh the pros and cons of further axillary dissection.

TABLE 3. *Studies reporting incidence of non-SLN metastases in axillae with positive SLN(s), by presence of LVI in primary tumor*

Author	No LVI	LVI
Reynolds[21]	43%	62%
Turner[25]	37%	65%
Abdessalem[23]	31%	62%
Rahusen[24]	42%	30%
Weiser[26]	26%	41%
Viale[28]	21%	26%
Sachdev[29]	12%	32%

LVI, lymphovascular invasion; SLN, sentinel lymph node.

MATERIALS AND METHODS

Between September 12, 1996, and September 20, 2002, 4790 consecutive cases of SLN biopsy at Memorial Sloan-Kettering Cancer Center (MSKCC) were entered prospectively into the MSKCC Breast Cancer Sentinel Lymph Node Database. Our study population involved the subset of 1075 cases that fulfilled the following criteria: primary invasive breast carcinoma with clinically negative axilla and no prior systemic treatment; successful SLN biopsy in which metastatic disease was identified; and completion ALND with at least 10 nodes examined. A total of 140 cases were excluded because a completion ALND was not performed. The overall study population comprised the patients meeting the selection criteria, who were then divided into two groups: a retrospective group who had undergone SLN biopsy between September 12, 1996, and April 24, 2001, and a prospective group undergoing SLN biopsy between April 25, 2001, and September 20, 2002. This project was reviewed and approved by the MSKCC Institutional Review Board.

TABLE 4. *Studies reporting incidence of non-SLN metastases in axillae with positive SLN(s), by size of SLN metastasis*

Author	<1 mm	≥1 mm	≤2 mm	>2 mm	>2 cm or "gross disease"
Chu[9]	—	—	7%	55%	—
Reynolds[21]	—	—	22%	67%	—
Turner[25]	—	—	26%	63%	—
Abdessalem[23]	—	—	20%	47%	75%
Kamath[10a]	—	—	15%	58%	65%
Rahusen[24]	27%	50%	—	—	—
Viale[28]	16%	—	22%	45%	—
Weiser[26]	—	—	18%	45%	—
Mignotte[30a]	—	—	22%	79%	—
Sachdev[29]	17%	49%	—	—	—

SLN, sentinel lymph node.
[a] Categories used: <2 mm and >2 mm.

TABLE 5. *Studies reporting incidence of non-SLN metastases in patients with IHC-detected SLN metastases*

Author	Proportion	%
Teng[22]	3/26	12
Kamath[10]	2/26	8
Wong[27]	3/28	11
Mignotte[30]	7/44	16
Jakub[31]	9/62	15

SLN, sentinel lymph node; IHC, immunohistochemistry.

Our technique for SLN biopsy includes the use of both blue dye and radioisotope, as previously outlined in earlier studies at our institution.[33]

SLN Histopathological Evaluation

Whenever possible, the SLN was bisected and sectioned at 2–3-mm intervals. The nodal tissue was quick-frozen in liquid nitrogen, and a single 5-μm-thick section stained with hematoxylin and eosin (H&E) was examined intraoperatively (frozen-section analysis). If the section was positive, a complete ALND was done immediately. After the frozen-section analysis, the remaining frozen tissue was fixed in formalin and embedded in paraffin. Another 5-μm-thick H&E-stained section was evaluated as a frozen-section control (routine histopathology). If this section showed evidence of metastatic disease, no further pathological workup of the SLN was performed. If the routine H&E section remained negative, enhanced pathological analysis was performed in the following fashion: two pairs of H&E- and cytokeratin IHC–stained sections with a distance of 50 μm between the pairs were prepared from the paraffin block. At one level, the cytokeratin antibody CAM 5.2 (Becton Dickinson Immunocytometry Systems, San Jose, CA) was used, whereas the cytokeratin cocktail AE1:AE3 (Ventana Medical Systems, Tucson, AZ) was applied for the other level. Patients with SLN metastases not detected by frozen-section analysis generally underwent completion ALND at a later date. For all additional nodes identified by completion ALND, routine H&E analysis was done on a single section of each node.

Data Analysis

Clinical data collected for each case from the database included age; pathological size of the invasive carcinoma, defined in centimeters; tumor type (ductal or lobular carcinoma); nuclear grade (I: slight or no variation in size and shape of nucleus; II: moderate variation in size and shape; III: marked variation in size and shape); presence of lymphovascular invasion (presence of one or more tumor cells in a lymphatic or vascular structure); multifocality of primary tumor (foci of carcinoma separate from primary tumor); estrogen-receptor (ER) status (negative, <10% of cells staining positive); method of detection of SLN metastases (frozen-section analysis [frozen], routine histopathology [routine], H&E stains of serial sections [serial HE], IHC); number of

TABLE 6. *Descriptive characteristics of the retrospective (9/12/1996–4/24/2001) and prospective (4/25/2001–9/20/2002) patient populations*

	Retrospective (n = 702)		Prospective (n = 373)	
	n	%	n	%
Age				
≤50	290	41.3	157	42.1
>50	412	58.7	216	57.9
Pathologic size (cm)				
≤.5	33	4.7	13	3.5
.6–1.0	122	17.4	49	13.1
1.1–2.0	312	44.4	166	44.5
2.1–3.0	154	21.9	93	24.9
3.1–5.0	65	9.3	41	11.0
≥5.1	16	2.3	11	2.9
Tumor type and nuclear grade				
Ductal, I	22	3.1	11	2.9
Ductal, II	321	45.7	175	46.9
Ductal, III	275	39.2	129	34.6
Lobular	84	12.0	58	15.5
Lymphovascular invasion				
No	418	59.5	219	58.7
Yes	284	40.5	154	41.3
Multifocal				
No	505	71.9	241	64.6
Yes	197	28.1	132	35.4
Estrogen-receptor status				
Negative	135	19.2	83	22.3
Positive	567	80.8	290	77.7
Method of detection				
IHC only	63	9.0	18	4.8
Serial H&E	78	11.1	40	10.7
Routine H&E	65	9.3	23	6.2
Frozen	463	66.0	273	73.2
Frozen not done	33	4.7	19	5.1
No. of positive SLN				
1	488	69.5	265	71
2	161	22.9	75	20.1
3	35	5.0	21	5.6
4	12	1.7	8	2.1
5	3	.4	3	.8
6	1	.1	0	0
7	2	.3	0	0
≥8	0	0	1	.3
No. of negative SLN				
0	271	38.6	132	35.4
1	183	26.1	79	21.2
2	102	14.5	72	19.3
3	68	9.7	41	11.0
4	34	4.8	22	5.9
5	16	2.3	7	1.9
6	6	.9	10	2.7
7	8	1.1	2	.5
≥8	14	2.0	8	2.1

SLN, sentinel lymph node; IHC, immunohistochemistry; H&E, hematoxylin and eosin.

TABLE 7. *Incidence of additional, non-SLN metastases for retrospective and prospective patient populations, by primary and SLN pathologic characteristics*

	Retrospective (n = 702)		Prospective (n = 373)		Entire population (n = 1075)	
	Proportion	%	Proportion	%	Proportion	%
Age						
≤50	114/290	39	64/157	41	178/447	40
>50	150/412	36	90/216	42	240/628	38
Pathologic size (cm)						
≤.5	8/33	24	1/13	8	9/46	20
.6–1.0	32/122	26	13/49	26	45/171	26
1.1–2.0	111/312	36	60/166	36	171/478	36
2.1–3.0	62/154	40	44/93	47	106/247	43
3.1–5.0	37/65	57	26/41	63	63/106	59
≥5.1	14/16	88	10/11	91	24/27	89
Tumor type and nuclear grade						
Ductal, I	6/22	27	3/11	27	9/33	27
Ductal, II	100/321	31	57/175	33	157/496	32
Ductal, III	121/275	44	67/129	52	188/404	47
Lobular	37/84	44	27/58	47	64/142	45
Lymphovascular invasion						
No	125/418	30	71/219	32	196/637	31
Yes	139/284	49	83/154	54	222/438	51
Multifocality						
No	176/505	35	89/241	37	265/746	36
Yes	88/197	45	65/132	49	153/329	47
Estrogen-receptor status						
Negative	50/135	37	37/83	45	87/218	40
Positive	214/567	38	117/290	40	331/857	39
Method of detection						
IHC only	6/63	10	4/18	22	10/81	12
Serial H&E	12/78	15	3/40	8	15/118	13
Routine H&E	13/65	20	6/23	26	19/88	22
Frozen	221/463	48	128/273	47	349/736	47
Frozen not done	12/33	36	13/19	68	25/52	48
No. of positive SLN						
1	155/488	32	97/265	37	252/753	33
2	72/161	45	34/75	45	106/236	45
3	23/35	66	15/21	71	38/56	68
4	9/12	75	5/8	62	14/20	70
5	2/3	67	2/3	67	4/6	67
6	1/1	100	0/0	—	1/1	100
7	2/2	100	0/0	—	2/2	100
≥8	0/0	—	1/1	100	1/1	100
No. of negative SLN						
0	134/271	49	83/132	63	217/403	54
1	67/183	37	25/79	32	92/262	35
2	27/102	26	18/72	25	45/174	26
3	18/68	26	14/41	34	32/109	29
4	11/34	32	10/22	45	21/56	38
5	3/16	19	0/7	0	3/23	13
6	1/6	17	3/10	30	4/16	25
7	2/8	25	1/2	50	3/10	30
≥8	1/14	7	0/8	0	1/22	5

SLN, sentinal lymph node; IHC, immunohistochemistry; H&E, hematoxylin and eosin.

positive SLNs; and number of negative SLNs. Because lobular carcinomas generally are not assigned a nuclear grade, the tumor type and nuclear grade were combined into the following four categories: ductal carcinoma, nuclear grade I; ductal carcinoma, nuclear grade II; ductal carcinoma, nuclear grade III; and lobular carcinoma. To allow use of our model by groups that do not routinely perform frozen-section analysis, a second model was developed with only three levels for the method of detection variable: routine histopathology (routine), serial sectioning (serial HE), and immunohistochemistry (IHC). In this model, a node in which metastatic disease was detected by either frozen-section analysis or routine histopathology was categorized as routine. Data on ad-

ditional variables such as progesterone-receptor status, histologic grade, and AJCC T stage were also collected; however, because these variables are highly correlated with ER status, nuclear grade, and pathological size, respectively, they were not considered to be of substantial benefit to the model. HER-2/neu amplification data were also collected but were not included because they were incomplete and variable, owing to evolving methods of assessment during the years of the study.

A nomogram was developed based on the patients in the retrospective group and then was validated with the patients in the prospective group. In the retrospective population (n = 702), multivariable logistic regression was used to analyze the association of each variable with the likelihood of non-SLN metastases, and a nomogram was created with all variables. This model was used in the prospective group (n = 373) to predict each individual patient's probability of having positive non-SLNs. The discrimination of the model was measured by using the area under the receiver operating characteristic (ROC) curve. The calibration of the model was assessed graphically. Women were grouped into deciles based on their nomogram predictions. For each decile, the mean nomogram-predicted probability was compared with the proportion of women who actually had positive non-SLNs (actual probability). All analyses were performed with S-Plus Software Version 2000 Professional Edition with the Design Library (Mathsoft, Data Analysis Products Division, Seattle, WA).[34]

RESULTS

Descriptive characteristics of the study population are listed in Table 6. Table 7 shows the incidence of additional, non-SLN metastases for retrospective, prospective, and total patient populations by primary and SLN pathological characteristics. On multivariable logistic-regression analysis, pathological size, lymphovascular invasion, method of detection, number of positive SLNs, and number of negative SLNs were each associated with the likelihood of additional, non-SLN metastases ($P < .05$ for each). Multifocality was of borderline significance, and neither tumor type and nuclear grade nor ER status had a statistically significant association with the likelihood of non-SLN metastases (Tables 8 and 9). Age was not included in the final nomograms because its effect was too small to be seen on the nomograms.

A nomogram based on this model and developed in the retrospective population (n = 702) appears in Figure 1. The overall predictive accuracy of a model incorporating the eight variables, as measured by the bootstrap corrected ROC curve, was 0.76. To address the calibration accuracy of the nomogram (i.e., the absolute error of its prediction), we conducted additional bootstrapping and plotted the probabilities predicted by the nomogram against the corresponding observed proportions in the prospective population (n = 373) (Fig. 2). The area under the ROC curve for the model applied to the prospective population is 0.77. For those users who do not routinely perform frozen-section analysis on the SLN, a separate analysis without frozen-section information was performed and illustrated in the nomogram in Figure 3. The ROC of this version of the nomogram is 0.75 in the retrospective population and 0.78 in the

TABLE 8. *Results of multivariable logistic-regression analysis testing the relationship between primary tumor and SLN characteristics and the incidence of additional, non-SLN metastases*

Variables	*P* value
Pathology size	.001
Tumor type and nuclear grade	.7
Ductal, nuclear grade I vs. II	1.0
Ductal, nuclear grade I vs. III	.7
Ductal, nuclear grade I vs. lobular	.8
Lymphovascular invasion	.003
Multifocality	.06
Estrogen-receptor status	.08
Method of detection	<.001
Frozen vs. IHC	<.001
Frozen vs. serial HE	<.001
Frozen vs. routine	<.001
No. of positive SLN	<.001
No. of negative SLN	<.001

HE, hematoxylin and eosin; IHC, immunohistochemistry; SLN, sentinel lymph node.

TABLE 9. *Results of multivariable logistic-regression analysis testing the relationship between primary tumor and SLN characteristics and the incidence of non-SLN metastases*[a]

Variables	*P* value
Pathology size	.0006
Tumor type and nuclear grade	.4
Ductal, nuclear grade I vs. II	.8
Ductal, nuclear grade I vs. III	.4
Ductal, nuclear grade I vs. lobular	.6
Lymphovascular invasion	.003
Multifocality	.02
Estrogen-receptor status	.16
Method of detection (no frozen section available)	<.0001
Routine vs. IHC	.0001
Routine vs. serial H&E	<.001
No. of positive SLN	.0001
No. of negative SLN	<.0001

H&E, hematoxylin and eosin; IHC, immunohistochemistry; SLN, sentinel lymph node.

[a]This model is for use when no frozen section data is available.

Method of detection has three values: routine H&E, serial H&E and IHC.

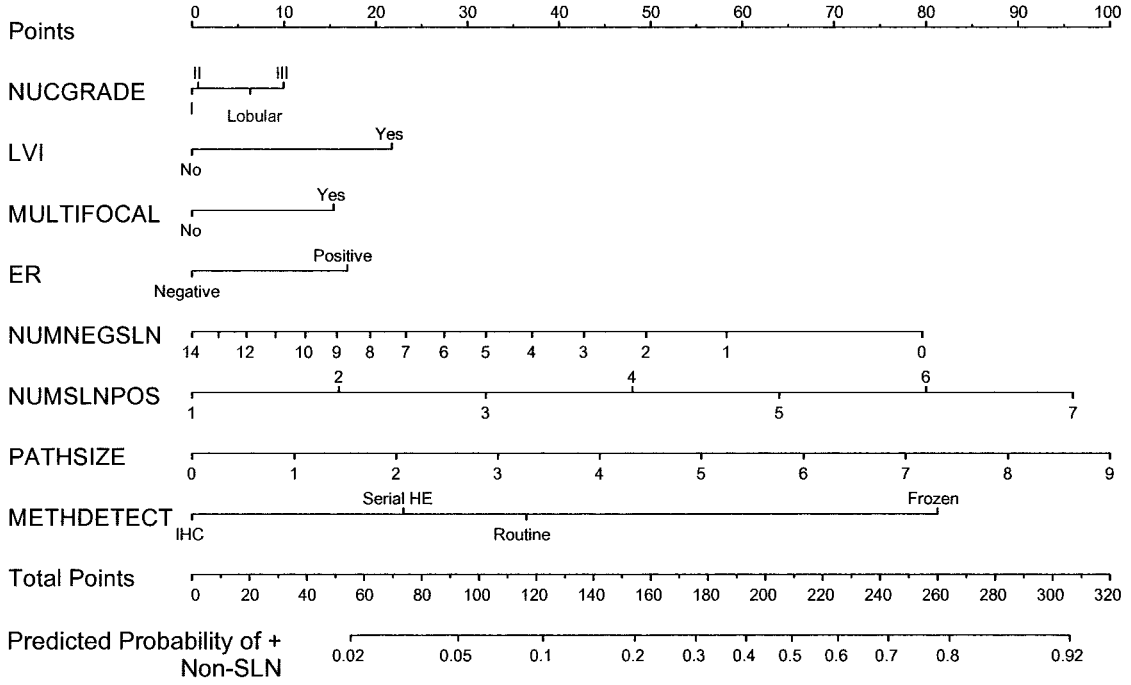

FIG. 1. Nomogram to predict likelihood of additional, non–sentinel lymph node (non-SLN) metastases in a patient with a positive SLN. NUCGRADE, tumor type and nuclear grade (ductal, nuclear grade I; ductal, nuclear grade II; ductal, nuclear grade III; lobular); LVI, lymphovascular invasion; MULTIFOCAL, multifocality of primary tumor; ER, estrogen-receptor status; NUMNEGSLN, number of negative SLNs; NUMSLNPOS, number of positive SLNs; PATHSIZE, pathological size, defined in centimeters; and METHDETECT, method of detection of SLN metastases (frozen, routine H&E, serial HE, IHC). The first row (POINTS) is the point assignment for each variable. Rows 2–9 represent the variables included in the model. For an individual patient, each variable is assigned a point value (uppermost scale, POINTS) based on the histopathological characteristics. A vertical line is made between the appropriate variable value and the POINTS line. The assigned points for all eight variables are summed, and the total is found in row 10 (TOTAL POINTS). Once the total is located, a vertical line is made between TOTAL POINTS and the final row, Row 11 (Predicted Probability of +non-SLN).

prospective population; the corresponding calibration curve is depicted in Figure 4.

Using the Nomogram

Each version of the nomogram consists of 11 rows. The first row (POINTS) is the point assignment for each variable. Rows 2 through 9 represent the variables included in the model. For an individual patient, each variable is assigned a point value (uppermost scale [POINTS]) based on the histopathological characteristics. To determine the point assignment, a vertical line is made between the appropriate variable value and the POINTS line. For example, a pathological size of 1 cm (PATHSIZE, 2) confers about 10 points.

The assigned points for all eight variables are summed, and the total is found in row 10 (TOTAL POINTS). Once the total is located in row 10 (TOTAL POINTS), a vertical line is made between it and the corresponding value in the final row, row 11 (Predicted Probability of +non-SLN). The version of the nomogram in Figure 1 is for use when information on frozen-section analysis is available; that in Figure 3 is for those cases where frozen-section information is not available.

In addition to the graphic nomograms, to facilitate ease of use in the clinical setting, we have made a personal digital assistant (PDA)–compatible application for use with hand-held Palm-type devices (Palm, Milpitas, CA). We will make these applications available at our Web site, www.mskcc.org/nomograms.

DISCUSSION

With the adoption of SLN biopsy, a new clinical conundrum has become commonplace: should a completion ALND be done for a patient with a positive SLN biopsy? This question is particularly difficult with regard to patients with micrometastatic disease, disease which was undetectable in the era prior to SLN biopsy. Other investigators have attempted to address this question and have identified risk factors for the presence of additional, non-SLN disease, but all such attempts are limited by the practical difficulty of simultaneously including several

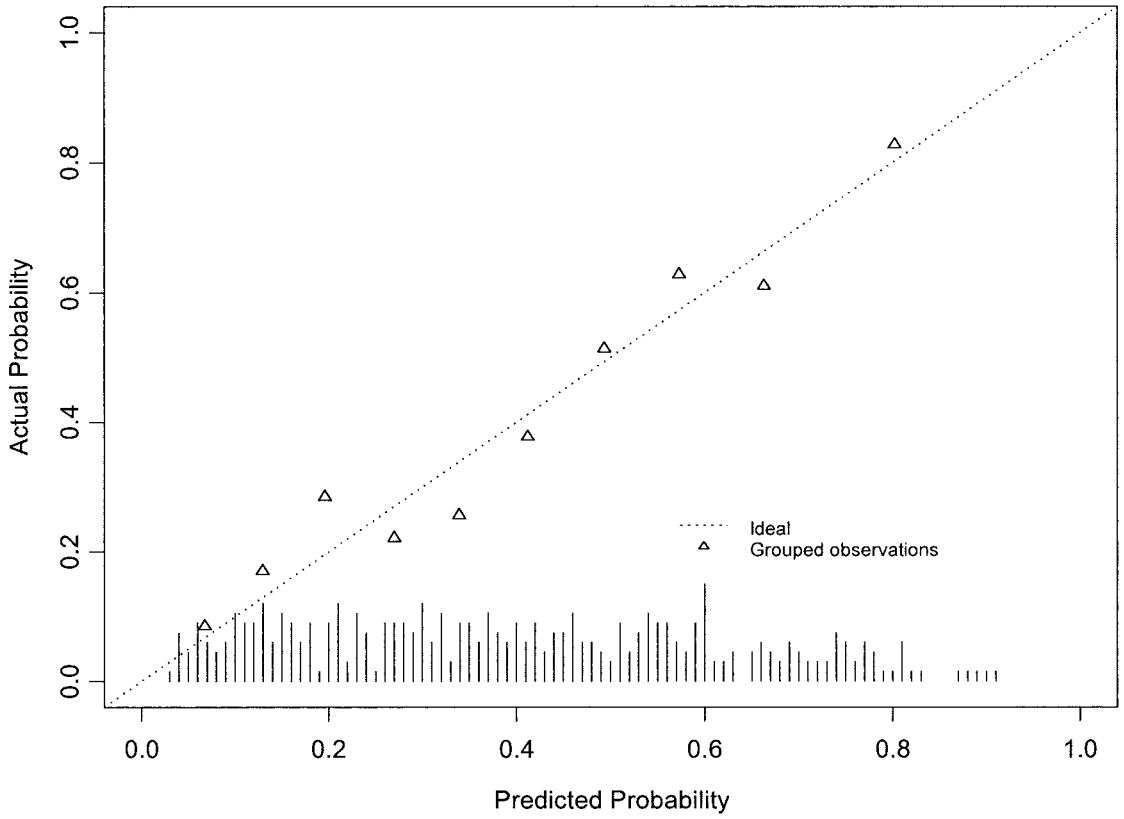

FIG. 2. Calibration plot for nomogram with frozen section information. The nomogram developed with use of the retrospective group of patients (n = 702) was applied to the prospective group (n = 373). A histogram of the calculated probabilities for the prospective population is shown along the horizontal axis. These 373 patients are grouped in deciles of their predicted probabilities, and the actual incidence of additional, non-SLN metastases was calculated for each decile. The vertical axis represents the actual, observed incidence (Actual Probability), and the horizontal axis represents the probability calculated by the nomogram (Predicted Probability). For each decile of the prospective group, a triangle is plotted to show actual probability. If the model were perfect, all triangles would lie on the dotted line, with a slope of 1.

variables in the risk estimate. Here, simultaneously using several variables in a large population, we have developed nomograms to predict the likelihood of additional nodal metastases after a positive SLN biopsy. We have prospectively tested them, demonstrating that they perform well in the prospective population.

Our nomograms utilize readily available clinical information and allow quick calculation. This approach may allow identification of extremely low-risk individuals for whom the risks associated with completion ALND are judged to outweigh the benefits. Conversely, our nomogram may allow identification of women at sufficient risk of additional nodal disease that they and their surgeon elect to proceed with completion ALND even though clinical "guesstimates" would suggest that they are at low risk.

The nomograms provide risk estimates that will have to be judged on an individual basis. A woman with a 1.8-cm, ER-positive, high-nuclear-grade ductal carcinoma with no LVI who has a single IHC-positive SLN might be considered to be at low risk. Our nomogram suggests that she has a 12% risk of having non-SLN metastases. Should she undergo completion ALND? Given this scenario, some will judge that a 12% risk of additional, non-SLN metastases justifies further ALND; others will not. The nomogram itself makes no actual treatment recommendations.

There are several limitations to our model. The nodes retrieved at completion ALND were examined by routine pathological analysis only. Other investigators[25,35] have shown that if non-SLNs are examined with serial sectioning and IHC, a higher proportion of patients with additional, non-SLN disease at completion ALND are identified. Evaluation by enhanced pathological analysis would clearly alter our model.

Furthermore, the clinical relevance of resecting additional nodal disease (even that detected by routine analysis) remains unknown. Although some argue that sur-

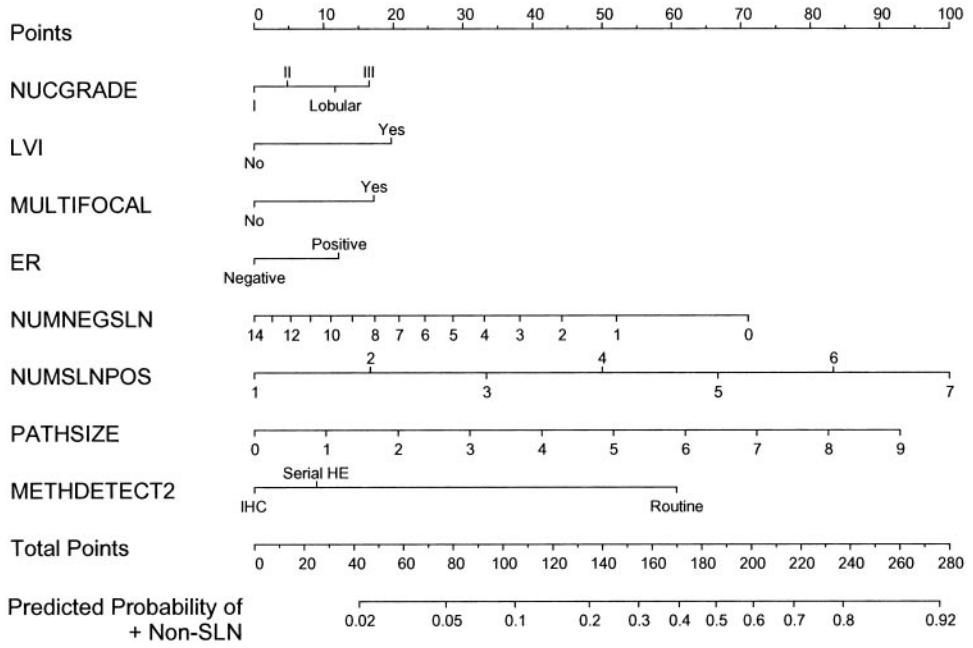

FIG. 3. Nomogram without frozen-section information, for use when frozen-section analysis is not done at the time of sentinel lymph node (SLN) biopsy. See Figure 1 legend for instructions on nomogram use. Routine, routine H&E.

gical removal of subclinical nodal disease is associated with a small but nonzero survival benefit, others argue that current adjuvant systemic therapy and radiation therapy would likely treat the majority of patients adequately. This study does not address this issue but provides accurate and individualized estimates of the likelihood of finding additional disease at completion ALND. The American College of Surgeons Oncology Group Protocol Z0011 (ACOSOG Z0011), currently under way and randomizing women with a positive SLN to undergo ALND or no ALND, is designed to address this question directly.

In addition, the prognostic significance of micrometastatic nodal disease is a subject of debate. In his 1997 review of the published literature, Dowlatshahi[36] concluded that all but one of the large ($N \geq 147$) and long-term ($\geq$6-year) studies demonstrated a statistically significant decrement in survival associated with micrometastatic disease. At MSKCC, Tan et al.[37] recently re-examined all axillary nodes from 373 patients treated in the 1970s who were deemed to be node-negative by routine histopathological analysis. Nodes were examined by serial sectioning and IHC, and the presence of any detectable micrometastatic disease was associated with worse disease-free and overall survival.

Another limitation of our data is the absence of size determination for the nodal metastases. The *AJCC Cancer Staging Manual*, 6th edition, now includes size of metastasis as an important determination of stage (and, therefore, of prognosis). However, we have had difficulty assigning a size to many cases because of the difference in pattern of distribution of malignant cells within the node. For example, some nodes may have scattered single cells or multiple small clusters of cells. How should these be measured? Ideally, an accurate estimate of volume could be assigned to each SLN metastasis. However, this is extremely time-consuming and somewhat impractical.

Nevertheless, it is clear that IHC is more sensitive than H&E in detecting micrometastases, that routine H&E analysis is more sensitive than frozen-section analysis, and that there is a correlation between method of detection and volume of disease. Others[10,24] have demonstrated quantitatively that method of detection is correlated with measured size of the SLN metastasis. Therefore, in order to have a consistent, practical, and reproducible methodology of estimation, the method of detection of the nodal metastasis was used. This provides a general estimate of the amount of nodal disease and allows categorizing into four distinct groups.

Another potential weakness in our data is that some of our patients, especially those with a perceived low risk of additional, non-SLN metastases, did not undergo a completion ALND and therefore were not included in our model. However, as demonstrated in the histograms (Figs. 2 and 4), the patients in the prospective population

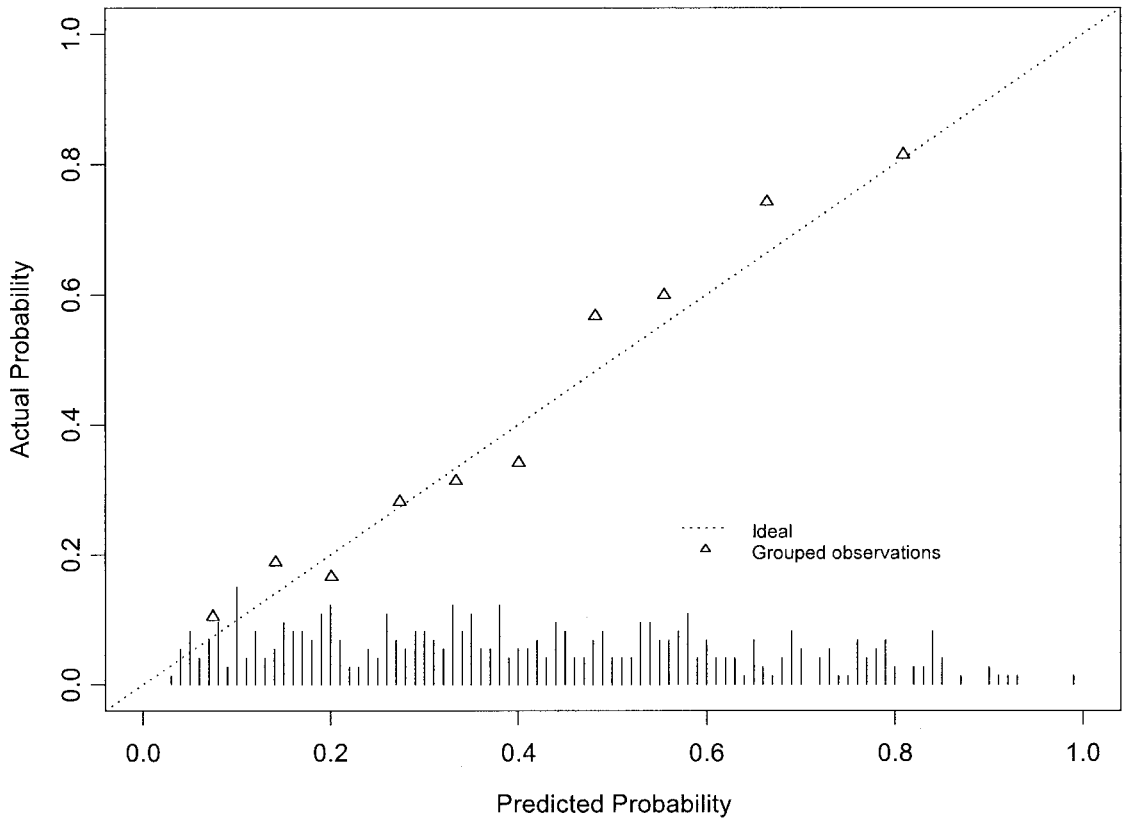

FIG. 4. Calibration plot for nomogram without frozen section data. The nomogram developed with use of the retrospective group of patients (n = 702) was applied to the prospective group (n = 373). A histogram of the calculated probabilities for the prospective population is shown along the horizontal axis. These 373 patients are grouped in deciles of their predicted probabilities, and the actual incidence of additional, non-SLN metastases was calculated for each decile. The vertical axis represents the actual, observed incidence (Actual Probability), and the horizontal axis represents the probability calculated by the nomogram (Predicted Probability). For each decile of the prospective group, a triangle is plotted to show actual probability. If the model were perfect, all triangles would lie on the dotted line, with a slope of 1.

are distributed quite evenly across the range of predicted risk. Furthermore, as demonstrated on the calibration curves, the models do predict well in the prospective population, even for those in the lowest decile of predicted risk.

Some might express surprise at the effect of ER status in the nomogram. Intuitively, one might expect ER positivity to be associated with lower risk of additional, non-SLN metastases. In our model, the effect of ER status is of only borderline statistical significance ($P = .08$), but it was included to improve the overall predictive ability of the model. Furthermore, although the finding is counterintuitive, others have reported similar findings. Nationwide data from the American College of Surgeons[38] also indicated that cases negative for ER had a lower risk of lymph node metastases, after adjustment for all other factors.

Last, our models are imperfect. For the first model, the area under the ROC curve was 0.77 for the prospective population. This means that if we randomly select two women, of whom one has at least one positive non-SLN and the other has negative non-SLNs, there is a 77% chance that the nomogram will predict a higher probability for the positive woman. This is a scale that ranges from 0.5, which would be achieved by tossing a coin, to 1.0, which would require perfect ability to tell the positive woman from the negative one.

Nevertheless, these models represent a significant improvement over estimates based on one or two variables in smaller populations. We have used our large, prospective database to develop the models and have proven their validity by testing them prospectively on a subsequent population. The calibration errors of our models are small (see Figs. 2 and 4), generally $<10\%$ across the spectrum of predictors. Other investigators have shown that removing statistically insignificant predictors actually worsens the predictive ability of the model.[39] Here, we have incorporated all statistically significant vari-

ables, as well as other clinically available and relevant variables, to provide improved prediction capability. Nomograms provide improved predictive ability in comparison with the crude counting of risk factors, and in addition, nomograms usually outperform clinical judgment, according to numerous studies conducted in other areas of medicine.[40]

With the important clinical question of whether to perform a completion ALND in a patient with a positive SLN biopsy arising more and more frequently, our nomograms provide an easy-to-use tool with which to simultaneously incorporate several important variables into the estimate of risk of additional, non-SLN metastases. Further validation and follow-up studies such as ACOSOG Z0011 will ultimately provide additional guidance to the clinician and patient. These nomograms provide a risk estimate that can help in weighing the pros and cons of completion ALND for an individual patient with SLN metastases.

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REFERENCES

1. Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997;15:2345–50.
2. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996;276:1818–22.
3. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997;349:1864–7.
4. O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg* 1998;186:423–7.
5. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med* 1998;339:941–6.
6. Veronesi U, Paganelli G, Viale G, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. *J Natl Cancer Inst* 1999;91:368–73.
7. Giuliano AE, Haigh PI, Brennan MB, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *J Clin Oncol* 2000;18:2553–9.
8. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg* 1997;226:271–8.
9. Chu KU, Turner RR, Hansen NM, Brennan MB, Bilchik A, Giuliano AE. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? *Ann Surg* 1999;229:536–41.
10. Kamath VJ, Giuliano R, Dauway EL, et al. Characteristics of the sentinel lymph node in breast cancer predict further involvement of higher-echelon nodes in the axilla. *Arch Surg* 2001;136:688–92.
11. Cabanes PA, Salmon RJ, Vilcoq JR, et al. Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. *Lancet* 1992;339:1245–8.
12. Moore MP, Kinne DW. Axillary lymphadenectomy: a diagnostic and therapeutic procedure. *J Surg Oncol* 1997;66:2–6.
13. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24,740 breast cancer cases. *Cancer* 1989;63:181–7.
14. American Joint Committee on Cancer. Breast. *AJCC Cancer Staging Manual*. 6th ed. New York: Springer, 2002:221–40.
15. Sosa JA, Diener-West M, Gusev Y, et al. Association between extent of axillary lymph node dissection and survival in patients with stage I breast cancer. *Ann Surg Oncol* 1998;5:140–9.
16. Hayward J, Caleffi M. The significance of local control in the primary treatment of breast cancer. *Arch Surg* 1987;122:1244–7.
17. Osteen RT, Harris JR. Patients with early breast cancer benefit from effective axillary treatment. *Breast Cancer Res Treat* 1985;5:17–21.
18. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival: a Bayesian meta-analysis. *Ann Surg Oncol* 1999;6:109–16.
19. Cady B. Case against axillary lymphadenectomy for most patients with infiltrating breast cancer. *J Surg Oncol* 1997;66:7–10.
20. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391–401.
21. Reynolds C, Rosemarie M, Donohue JH, et al. Sentinel lymph node biopsy with metastasis: can axillary dissection be avoided in some patients with breast cancer? *J Clin Oncol* 1999;17:1720–6.
22. Teng S, Dupont E, McCann C, et al. Do cytokeratin-positive-only sentinel lymph nodes warrant complete axillary lymph node dissection in patients with invasive breast cancer? *Am Surg* 2000;66:574–8.
23. Abdessalam SF, Zervos EE, Prasad M, et al. Predictors of positive axillary lymph nodes after sentinel lymph node biopsy in breast cancer. *Am J Surg* 2001;182:316–20.
24. Rahusen FD, Torrenga H, van Diest PJ, et al. Predictive factors for metastatic involvement of nonsentinel nodes in patients with breast cancer. *Arch Surg* 2001;136:1059–63.
25. Turner RR, Chu KU, Qi K, et al. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. *Cancer* 2000;89:574–81.
26. Weiser MR, Montgomery LL, Tan LK, et al. Lymphovascular invasion enhances the prediction of non-sentinel node metastases in breast cancer patients with positive sentinel nodes. *Ann Surg Oncol* 2001;8:145–9.
27. Wong SL, Edwards MJ, Chao C, et al. Predicting the status of the nonsentinel axillary nodes. *Arch Surg* 2001;136:563–8.
28. Viale G, Maiorano E, Mazzarol G, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. *Cancer* 2001;92:1378–84.
29. Sachdev U, Murphy K, Derzie A, Jaffer S, Bleiweiss IJ, Brower S. Predictors of nonsentinel lymph node metastasis in breast cancer patients. *Am J Surg* 2002;183:213–7.
30. Mignotte H, Treilleux I, Faure C, Nessah K, Bremond A. Axillary lymph-node dissection for positive sentinel nodes in breast cancer patients. *Eur J Surg Oncol* 2002;28:623–6.
31. Jakub JW, Diaz NM, Ebert MD, et al. Completion axillary lymph node dissection minimizes the likelihood of false negatives for patients with invasive breast carcinoma and cytokeratin positive only sentinel lymph nodes. *Am J Surg* 2002;184:302–6.
32. Czerniecki BJ, Scheff AM, Callans LS, et al. Immunohistochemistry with pancytokeratins improves the sensitivity of sentinel lymph node biopsy in patients with breast carcinoma. *Cancer* 1999;85:1098–103.

33. Cody HS III. Clinical aspects of sentinel node biopsy. *Breast Cancer Res* 2001;3:104–8.
34. Harrell FE Jr. *Regression Modeling Strategies With Applications to Linear Models, Logistic Regression, and Survival Analysis.* Springer Series in Statistics. New York: Springer-Verlag, 2001:568.
35. Chu KU, Turner RR, Hansen NM, Brennan MB, Giuliano AE. Sentinel node metastasis in patients with breast carcinoma accurately predicts immunohistochemically detectable nonsentinel node metastasis. *Ann Surg Oncol* 1999;6:756–61.
36. Dowlatshahi K, Fan M, Snider HC, Habib FA. Lymph node micrometastases from breast carcinoma: reviewing the dilemma. *Cancer* 1997;80:1188–97.
37. Tan LK, Giri D, Panageas K, et al. Occult/micrometastases in axillary lymph nodes of breast cancer patients are significant: a retrospective study with long-term follow-up [abstract]. *Proc Am Soc Clin Oncol* 2002;21:37a.
38. Gann PH, Colilla SA, Gapstur SM, Winchester DJ, Winchester DP. Factors associated with axillary lymph node metastasis from breast carcinoma: descriptive and predictive analyses. *Cancer* 1999;86:1511–9.
39. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
40. Ross PL, Gerigk C, Gonen M, et al. Comparisons of nomogram and urologists' predictions in prostate cancer. *Semin Urol Oncol* 2002;20:82–8.